

Measles is an acute viral infectious disease. There are references to measles as early as the 7th century. The disease was described by Rhazes in the 10th century as “more dreaded than smallpox.”

In 1846, Peter Panum described the incubation period of measles and lifelong immunity. Enders and Peebles isolated the virus in human and monkey kidney tissue culture in 1954. The first live attenuated vaccine was licensed for use in the U.S. in 1963 (Edmonston B strain).

Before a vaccine was available, infection with measles virus was nearly universal during childhood with more than 90% of persons immune by age 15 years. Measles is a common and often fatal disease in developing countries. The World Health Organization estimates there were 30-40 million cases and 745,000 deaths from measles in 2001.

MEASLES VIRUS

The measles virus is a paramyxovirus, genus Morbillivirus. It is 100 to 200 nm in diameter, with a core of single-stranded RNA, and is closely related to the rinderpest and canine distemper viruses. Two membrane envelope proteins are important in pathogenesis. They are the F (fusion) protein, which is responsible for fusion of virus and host cell membranes, viral penetration, and hemolysis, and the H (hemagglutinin) protein which is responsible for adsorption of virus to cells.

There is only one antigenic type of measles virus. Although studies have documented changes in the H glycoprotein, these changes do not appear to be epidemiologically important (*i.e.*, no change in vaccine efficacy has been observed).

Measles virus is rapidly inactivated by heat, light, acidic pH, ether, and trypsin. It has a short survival time (<2 hours) in the air, or on objects and surfaces.

PATHOGENESIS

Measles is a systemic infection. The primary site of infection is the respiratory epithelium of the nasopharynx. Two to three days after invasion and replication in the respiratory epithelium and regional lymph nodes, a primary viremia occurs with subsequent infection of the reticuloendothelial system. Following further viral replication in regional and distal reticuloendothelial sites, there is a second viremia, which occurs 5 to 7 days after initial infection. During this viremia, there may be infection of the respiratory tract and other organs. Measles virus is shed from the nasopharynx beginning with the prodrome until 3-4 days after rash onset.

CLINICAL FEATURES

The **incubation period** of measles, from exposure to prodrome averages 10-12 days. From exposure to rash onset averages 14 days (range, 7-18 days).

Measles

- Highly contagious viral illness
- First described in 7th century
- Near universal infection of childhood in prevaccination era
- Frequent and often fatal in developing areas

Measles Virus

- Paramyxovirus (RNA)
- Hemagglutinin important surface antigen
- One antigenic type
- Rapidly inactivated by heat and light

Measles Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Primary viremia 2-3 days after exposure
- Secondary viremia 5-7 days after exposure with spread to tissues

Measles Clinical Features

- Incubation period 10-12 days
- Prodrome**
- Stepwise increase in fever to 103 F or higher
- Cough, coryza, conjunctivitis
- Koplik's spots

Measles Clinical Features

Rash

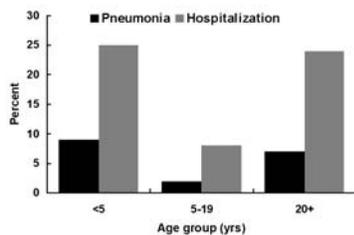
- 2-4 days after prodrome, 14 days after exposure
- Maculopapular, becomes confluent
- Begins on face and head
- Persists 5-6 days
- Fades in order of appearance

Measles Complications

Condition	Percent reported
Diarrhea	8
Otitis media	7
Pneumonia	6
Encephalitis	0.1
Death	0.2
Hospitalization	18

Based on 1985-1992 surveillance data

Measles Complications by Age Group



The **prodrome** lasts 2-4 days (range 1-7 days). It is characterized by fever, which increases in stepwise fashion, often peaking as high as 103°-105°F. This is followed by the onset of cough, coryza (runny nose), and/or conjunctivitis.

Koplik's spots, a rash (enanthem) present on mucous membranes, is considered to be pathognomonic for measles. It occurs 1-2 days before the rash to 1-2 days after the rash, and appears as punctate blue-white spots on the bright red background of the buccal mucosa.

The measles **rash** is a maculopapular eruption that usually lasts 5-6 days. It begins at the hairline, then involves the face and upper neck. During the next 3 days, the rash gradually proceeds downward and outward, reaching the hands and feet. The maculopapular lesions are generally discrete, but may become confluent, particularly on the upper body. Initially, lesions blanch with fingertip pressure. By 3-4 days, most do not blanch with pressure. Fine desquamation occurs over more severely involved areas. The rash fades in the same order that it appears, from head to extremities.

Other symptoms of measles include anorexia, diarrhea, especially in infants, and generalized lymphadenopathy.

COMPLICATIONS

Approximately 30% of reported measles cases have one or more complications. Complications of measles are more common among children <5 and adults >20 years of age.

From 1985 through 1992, **diarrhea** was reported in 8% of reported cases, making this the most commonly reported complication of measles. **Otitis media** was reported in 7% of reported cases and occurs almost exclusively in children. **Pneumonia** (6% of reported cases) may be viral or superimposed bacterial, and is the most common cause of death.

Acute **encephalitis** is reported in approximately 0.1% of reported cases. Onset generally occurs 6 days after rash onset (range 1-15 days), and is characterized by fever, headache, vomiting, stiff neck, meningeal irritation, drowsiness, convulsions, and coma.

Cerebrospinal fluid shows pleocytosis and elevated protein. Case fatality rate is approximately 15%. Some form of residual neurologic damage occurs in as many as 25%. **Seizures** (with or without fever) are reported in 0.6% to 0.7% of reported cases.

Death from measles has been reported in approximately 1-2 per 1,000 reported cases in the United States in recent years. As with other complications of measles, the risk of death is higher among young children and adults. Pneumonia accounts for about 60% of deaths. The most common causes of death are pneumonia in children and acute encephalitis in adults.

Subacute sclerosing panencephalitis (SSPE) is a rare degenera-

tive central nervous system disease believed to be due to persistent measles virus infection of the brain. Average onset occurs 7 years after measles (range 1 month–27 years), and occurs in five to ten cases per million reported measles cases. The onset is insidious, with progressive deterioration of behavior and intellect, followed by ataxia (awkwardness), myoclonic seizures, and eventually death. SSPE has been extremely rare since the early 1980s.

Measles illness during pregnancy results in a higher risk of premature labor, spontaneous abortion, and low-birth-weight infants. Birth defects (with no definable pattern of malformation) have been reported rarely, without confirmation that measles was the cause.

Atypical measles occurs only in persons who received inactivated (“killed”) measles vaccine (KMV) and are subsequently exposed to wild type measles virus. An estimated 600,000 to 900,000 persons received KMV in the U.S. from 1963 to 1967. KMV sensitized the recipient to measles virus antigens without providing protection. Subsequent infection with measles virus leads to signs of hypersensitivity polyserositis. The illness is characterized by fever, pneumonia, pleural effusions, and edema. The rash is usually maculopapular or petechial, but may have urticarial, purpuric, or vesicular components. It appears first on the wrists or ankles. Atypical measles may be prevented by revaccinating with live measles vaccine. Moderate to severe local reactions with or without fever may follow vaccination; these reactions are less severe than with infection with wild measles virus.

Modified measles occurs primarily in patients who received immune globulin (IG) as post-exposure prophylaxis and in young infants who have some residual maternal antibody. It is usually characterized by a prolonged incubation period, mild prodrome, and sparse, discrete rash of short duration. Similar mild illness has been reported among previously vaccinated persons.

Rarely reported in the United States, **hemorrhagic measles** is characterized by high fever (105°–106°F), seizures, delirium, respiratory distress, and hemorrhage into the skin and mucous membranes.

Measles in an immunocompromised person may be severe, with a prolonged course. It is reported almost exclusively in persons with T-cell deficiencies (certain leukemias, lymphomas, and Acquired Immune Deficiency Syndrome [AIDS]). It may occur without the typical rash, and a patient may shed virus for several weeks after the acute illness.

Measles in developing countries has resulted in high attack rates among children <12 months of age. Measles is more severe in malnourished children, particularly those with vitamin A deficiency. Complications include diarrhea, dehydration, stomatitis, inability to feed, and bacterial infections (skin and elsewhere). The case fatality rate may be as high as 25%. Measles is also a leading cause of blindness in African children.

Measles Laboratory Diagnosis

- Isolation of measles virus from a clinical specimen (e.g., nasopharynx, urine)
- Significant rise in measles IgG by any standard serologic assay (e.g., EIA, HA)
- Positive serologic test for measles IgM antibody

LABORATORY DIAGNOSIS

Isolation of measles virus is not recommended as a routine method to diagnose measles. However, virus isolates are extremely important for molecular epidemiologic surveillance to help determine the geographic origin of the virus and the viral strains circulating in the United States.

Measles virus can be isolated from urine, nasopharyngeal aspirates, heparinized blood, or throat swabs. Specimens for virus culture should be obtained from every clinically suspected case of measles and should be shipped to the state public health laboratory or CDC, at the direction of the state health department. Clinical specimens for viral isolation should be collected at the same time as samples taken for serologic testing. Because the virus is more likely to be isolated when the specimens are collected within 3 days of rash onset, collection of specimens for virus isolation should not be delayed until serologic confirmation is obtained. Clinical specimens should be obtained within 7 days of rash onset, and should not be collected more than 10 days after rash onset. A detailed protocol for collection of specimens for viral isolation is available from the CDC.

Serologic testing, most commonly by enzyme-linked immunoassay (ELISA or EIA), is widely available and may be diagnostic if done at the appropriate time. Generally, a previously susceptible person exposed to either vaccine or wild type measles virus will first mount an IgM response and then an IgG response. The IgM response will be transient (1–2 months) and the IgG response should persist for many years. Uninfected persons should be IgM negative and will be either IgG negative or IgG positive depending upon their previous infection history.

ELISA tests for IgM antibody require only a single serum specimen and are diagnostic if positive. The preferred reference test is a capture IgM test developed by CDC, but currently there are indirect IgM assays that perform equally well. This test should be used to confirm every case of measles that is reported to have some other type of laboratory confirmation. IgM capture tests for measles are often positive on the day of rash onset. However, in the first 72 hours after rash onset, up to 20% of tests for IgM may give false-negative results. Tests that are negative in the first 72 hours after rash onset should be repeated. IgM is detectable for at least 28 days after rash onset and frequently longer.

A variety of tests for IgG antibodies to measles are available and include ELISA tests, hemagglutination inhibition, indirect fluorescent antibody tests, microneutralization, and plaque reduction neutralization. Complement fixation, while widely used in the past, is no longer recommended.

IgG testing for acute measles requires the demonstration of a rise in the titer of antibody against measles virus, so two serum specimens

are always required. The first specimen should be drawn as soon after rash onset as possible. The second specimen should be drawn 10–30 days later. The tests for IgG antibody should be conducted on both specimens at the same time. The same type of test should be used on both specimens. The specific criteria for documenting an increase in titer depends on the test.

Tests for IgG antibody require two serum specimens and a confirmed diagnosis cannot be made until the second specimen is obtained. As a result, IgM tests are generally preferred to confirm the diagnosis of measles.

EPIDEMIOLOGY

OCCURRENCE

Measles occurs throughout the world. However, interruption of indigenous transmission of measles has been achieved in the U.S. and other parts of the Western hemisphere.

RESERVOIR

Measles is a human disease. There is no known animal reservoir, and an asymptomatic carrier state has not been documented.

TRANSMISSION

Measles transmission is primarily person to person via large respiratory droplets. Airborne transmission via aerosolized droplet nuclei has been documented in closed areas (*e.g.*, office examination room) for up to 2 hours after a person with measles occupied the area.

TEMPORAL PATTERN

In temperate areas, measles disease occurs primarily in the late winter and spring.

COMMUNICABILITY

Measles is highly communicable, with >90% secondary attack rates among susceptible persons. Measles may be transmitted from 4 days prior to 4 days after rash onset. Maximum communicability occurs from onset of prodrome through the first 3-4 days of rash.

SECULAR TRENDS IN THE UNITED STATES

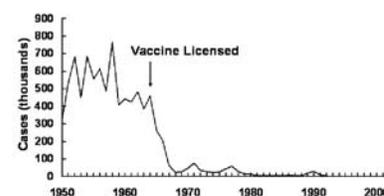
Before 1963, approximately 500,000 cases and 500 deaths were reported annually with epidemic cycles every 2-3 years. However, the actual number of cases was estimated at 3-4 million annually. More than 50% of persons had measles by age 6 and more than 90% had measles by age 15. The highest incidence was in 5-9 year-olds, who generally accounted for more than 50% of reported cases.

Following licensure of vaccine in 1963, the incidence of measles

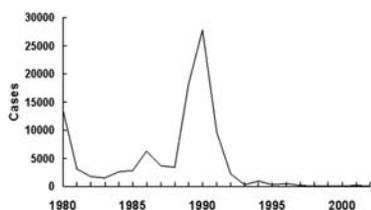
Measles Epidemiology

- Reservoir Human
- Transmission Respiratory
 Airborne
- Temporal pattern Peak in late winter and spring
- Communicability 4 days before to 4 days after
 rash onset

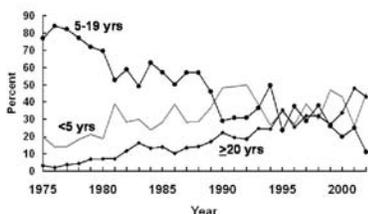
Measles – United States, 1950-2002



Measles – United States, 1980-2002



Age Distribution of Reported Measles, 1975-2002



Measles Resurgence – United States, 1989-1991

- Cases **55,622**
- Age group affected **Children <5 yrs**
- Hospitalizations **>11,000**
- Deaths **123**
- Direct medical costs **>\$150 million**

decreased by more than 98%, and 2-3 year epidemic cycles no longer occurred. Because of this success, a 1978 Measles Elimination Program set a goal to eliminate indigenous measles by October 1, 1982 (26,871 cases were reported in 1978). The 1982 elimination goal was not met, but in 1983, only 1,497 cases were reported (0.6 cases per 100,000 population), the lowest annual total ever reported up to that time.

During 1980-1988, a median of 57% of reported cases were among school-aged persons (5-19 years of age), and a median of 29% were among children <5 years of age. A median of 8% of cases were among infants <1 year of age.

From 1985 through 1988, 42% of cases occurred in persons who were vaccinated on or after their first birthday. During these years, 68% of cases in school-aged children (5-19 years) had been appropriately vaccinated. The occurrence of measles among previously vaccinated children (*i.e.*, vaccine failure) led to the recommendation for a second dose in this age group.

MEASLES RESURGENCE IN 1989-1991

In 1989 through 1991, a dramatic increase in cases occurred. During these 3 years a total of 55,622 cases were reported (18,193 in 1989; 27,786 in 1990; 9,643 in 1991). In addition to the increased number of cases, a change in age distribution of cases occurred. Prior to the resurgence, school-aged children had accounted for the largest proportion of reported cases. During the resurgence, 45% of all reported cases were in children <5 years of age. In 1990, 48% of patients were in this age group, the first time that the proportion of cases in children <5 years of age exceeded the proportion of cases in 5-19-year-olds. Thirty-five percent of cases were among school-aged persons (5-19 years old).

Overall incidence rates were highest for Hispanics and blacks and lowest for non-Hispanic whites. Among children <5 years of age the incidence of measles among blacks and Hispanics was four to seven times higher than among non-Hispanic whites.

A total of 123 measles-associated deaths were reported (death-to-case ratio = 2.2 per 1,000 cases). Forty-nine percent of deaths were among children <5 years of age. Ninety percent of fatal cases had no history of vaccination. Sixty-four deaths were reported in 1990, the largest annual number of deaths from measles since 1971.

The most important cause of the measles resurgence of 1989-1991 was low vaccination coverage. Measles vaccine coverage was low in many cities, including some that experienced large outbreaks among preschool-aged children throughout the early to mid-1980s. Surveys in areas experiencing outbreaks among preschool-aged children indicated that as few as 50% of children had been vaccinated against measles by their second birthday, and that black and Hispanic children were less likely to be age-appropriately vaccinated than white children.

Measles susceptibility of infants less than one year of age may have increased. During the 1989-1991 measles resurgence, incidence rates for infants were more than twice as high as those in any other age group. The mothers of many infants who developed measles were young, and their measles immunity was most often due to vaccination rather than infection with wild virus. As a result, a smaller amount of antibody was transferred across the placenta to the fetus, compared with antibody transfer from mothers who had higher antibody titers resulting from wild virus infection. The lower quantity of antibody resulted in immunity that waned more rapidly, making infants susceptible at a younger age than in the past.

The increase in measles in 1989-1991 was not limited to the United States. Large outbreaks of measles were reported by many other countries of North and Central America, including Canada, El Salvador, Guatemala, Honduras, Jamaica, Mexico, and Nicaragua.

MEASLES SINCE 1993

Reported cases of measles declined rapidly after the 1989-1991 resurgence. This decline was due primarily to intensive efforts to vaccinate preschool-aged children. Measles vaccination levels among 2 year-old children increased from 70% in 1990 to 91% in 1997.

Since 1993, fewer than 500 cases have been reported annually, and fewer than 200 cases per year have been reported since 1997. A record low annual total of 44 cases was reported in 2002. Available epidemiologic and virologic data strongly suggest that measles transmission in the United States has been interrupted. The majority of cases are now imported from other countries, or linked to imported cases. Most imported cases originate in Asia and Europe, and occur both among U.S. citizens traveling abroad and persons visiting the U.S. from other countries. Due to an aggressive measles vaccination program by the Pan American Health Organization, measles incidence is now very low in Latin America and the Caribbean. Measles elimination from the Americas appears to be an achievable goal.

Since the mid-1990s, no age group has predominated among reported cases of measles. Relative to earlier decades, an increased proportion of cases now occur among adults. In 1973, persons over 20 years of age and older accounted for only about 3% of cases. In 1994, adults accounted for 24% of cases, and in 2001, this age group accounted for 48% of all reported cases.

The size and makeup of measles outbreaks has changed since the 1980s. Prior to 1989, the majority of outbreaks occurred among middle, high school and college student populations. As many as 95% of persons infected during these outbreaks had received one prior dose of measles vaccine. A second dose of measles vaccine was recommended for school-aged children in 1989, and 49 states now require two doses of measles vaccine for school-aged children. As a result, measles outbreaks in school settings are now uncommon.

Measles 1993-2002

- Endemic transmission interrupted
- Record low annual total in 2002 (44 total cases)
- Many cases among adults
- Most cases imported or linked to importation

During the measles resurgence of 1989-1991, outbreaks among preschool-aged children became more prominent. More than 200 outbreaks were reported during each of these years, several of which included more than 1,000 cases. The largest outbreak involving predominantly unvaccinated preschool-aged children was in metropolitan Los Angeles, California. More than 12,000 measles cases were reported during this outbreak, which continued for almost 5 years (1987-1992). The last large outbreak involving preschool-aged children was reported in 1992.

Since 1993, the largest outbreaks of measles have occurred in populations that refuse vaccination for religious or personal belief reasons, including communities in Utah and Nevada, and Christian Scientist schools in Missouri and Illinois. Most outbreaks have involved limited spread from measles imported from outside the United States. The largest outbreak in 2000 involved 9 persons in New York.

In 2003, a large measles outbreak occurred in the Marshall Islands. As of December 2003, a total of 828 cases had been reported with 83 measles-related hospitalizations and 3 deaths. The outbreak affected predominantly preschool-aged children (40% of cases); adults 20 years and older accounted for 35% of cases. The virus isolated from one case (H1 genotype) was similar to a virus known to circulate in Japan, Korea, and China. A contributing factor for the outbreak was low age-specific measles vaccination coverage in young children, making this outbreak similar to those occurring among this age group on the mainland U.S. in the early 1990s. The outbreak was controlled with aggressive case finding and large vaccination campaigns targeting all persons 6 months to 40 years of age.

CLASSIFICATION OF MEASLES CASES

CLINICAL CLASSIFICATION OF MEASLES CASES

A **suspect case** is a person with a febrile illness accompanied by a generalized maculopapular rash.

A **probable case** meets the **measles case definition** of generalized maculopapular rash lasting ≥ 3 days, with fever $\geq 38.3^{\circ}\text{C}$ (101°F); and cough, or coryza, or conjunctivitis and has no or non-contributory serologic or virologic testing, and is not epidemiologically linked to a confirmed case. A **confirmed case** meets the case definition, and is epidemiologically linked to another confirmed or probable case; or is laboratory confirmed. A laboratory confirmed case does not need to meet the clinical case definition.

Only confirmed cases should be reported to CDC, but confirmed and probable cases should be reported as soon as possible to the local or state health department.

EPIDEMIOLOGIC CLASSIFICATION

An international **imported case** has its source outside the country,

Measles Clinical Case Definition

- Generalized rash lasting ≥ 3 days, and
- Temperature $\geq 38.3^{\circ}\text{C}$ (101°F), and
- Cough or coryza or conjunctivitis

rash onset occurs within 21 days after entering the country, and illness cannot be linked to local transmission.

An **indigenous case** is any case that cannot be proved to be imported. Subclasses of indigenous cases exist; for more information, see CDC Manual for Surveillance of Vaccine-Preventable Diseases (available on the NIP website at <http://www.cdc.gov/nip/publications/surv-manual/default.htm>).

MEASLES VACCINE

Measles virus was first isolated by John Enders in 1954. The first measles vaccines were licensed in 1963. In that year, both an inactivated (“killed”) and a live attenuated vaccine (Edmonston B strain) were licensed for use in the United States. The inactivated vaccine was withdrawn in 1967 because it did not protect against measles virus infection. Furthermore, recipients of inactivated measles vaccine frequently developed a unique syndrome, atypical measles, if infected with wild type measles virus (see Atypical Measles, above). The original Edmonston B vaccine was withdrawn in 1975, because of a relatively high frequency of fever and rash in recipients. A live, further attenuated vaccine (Schwarz strain) was first introduced in 1965, but also is no longer used in the United States. Another live, further attenuated strain vaccine (Edmonston-Enders strain) was licensed in 1968. These further attenuated vaccines caused fewer reactions than the original Edmonston B vaccine.

CHARACTERISTICS

The only measles virus vaccine now available in the United States is a live, more attenuated Edmonston-Enders strain (formerly called “Moraten”). The vaccine is available as a single antigen preparation, combined with rubella vaccine, or combined with mumps and rubella vaccines. The ACIP recommends that combined measles-mumps-rubella vaccine (MMR) be used when any of the individual components is indicated.

Measles vaccine is prepared in chick embryo fibroblast tissue culture. MMR is supplied as a lyophilized (freeze-dried) powder and is reconstituted with sterile, preservative-free water. The vaccine contains a small amount of human albumin, neomycin, sorbitol, and gelatin.

IMMUNOGENICITY AND VACCINE EFFICACY

Measles vaccine produces an inapparent or mild, noncommunicable infection. Measles antibodies develop in approximately 95% of children vaccinated at 12 months of age and 98% of children vaccinated at 15 months of age. Approximately 2%-5% of children who receive only one dose of MMR vaccine fail to respond to it (*i.e.*, primary vaccine failure). MMR vaccine failure may occur because of passive antibody in the vaccine recipient, damaged vaccine, incorrect records, and possibly other reasons. Most persons who fail to respond to the first dose will respond to a second dose. Studies

Measles Vaccines

1963	Live attenuated and killed vaccines
1965	Live further attenuated vaccine
1967	Killed vaccine withdrawn
1968	Live further attenuated vaccine (Edmonston-Enders strain)
1971	Licensure of combined measles-mumps-rubella vaccine
1989	Two dose schedule

Measles Vaccine

- **Composition** Live virus
- **Efficacy** 95% (range, 90%-98%)
- **Duration of Immunity** Lifelong
- **Schedule** 2 doses
- **Should be administered with mumps and rubella as MMR**

MMR Vaccine Failure

- **2%-5% of recipients do not respond to the first dose**
- **Caused by antibody, damaged vaccine, record errors**
- **Most persons with vaccine failure will respond to second dose**

Measles (MMR) Vaccine Indications

- All infants >12 months of age
- Susceptible adolescents and adults without documented evidence of immunity

Measles Mumps Rubella Vaccine

- 12 months is the recommended and minimum age
- MMR given before 12 months should not be counted as a valid dose
- Revaccinate at ≥ 12 months of age

Second Dose of Measles Vaccine

- Intended to produce measles immunity in persons who failed to respond to the first dose (primary vaccine failure)
- May boost antibody titers in some persons

Second Dose Recommendation

- First dose of MMR at 12-15 months
- Second dose of MMR at 4-6 years
- Second dose may be given any time >4 weeks after the first dose

indicate that more than 99% of persons who receive two doses of measles vaccine (with the first dose administered no earlier than the first birthday) develop serologic evidence of measles immunity.

Although the titer of vaccine-induced antibodies is lower than that following natural disease, both serologic and epidemiologic evidence indicate that vaccine-induced immunity appears to be long-term and probably life long in most individuals. Most vaccinated persons who appear to lose antibody show an anamnestic immune response upon revaccination indicating that they are probably still immune. Although revaccination can increase antibody titer in some persons, available data indicate that the increased titer may not be sustained. Some studies indicate that secondary vaccine failure (waning immunity) may occur after successful vaccination, but this appears to occur rarely and to only play a minor role in measles transmission and outbreaks.

VACCINATION SCHEDULE AND USE

Two doses of measles vaccine, as combination MMR, separated by at least 4 weeks, are routinely recommended for all children. All persons born in or after 1957 should have documentation of at least one dose of MMR or other evidence of measles immunity (see below). Certain adolescents and adults should receive 2 doses of MMR.

The first dose of MMR should be given on or after the first birthday. Any dose of measles-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with measles-containing vaccine before 12 months of age should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is at least 12 months of age.

A second dose of MMR is recommended to produce immunity in those who failed to respond to the first dose. The second dose of MMR vaccine should routinely be given at age 4-6 years, before a child enters kindergarten or first grade. The preadolescent health visit at age 11-12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR.

The second dose of MMR may be administered as soon as one month (*i.e.*, minimum of 28 days) after the first dose. Children who have already received two doses of MMR vaccine at least 4 weeks apart, with the first dose administered no earlier than the first birthday, do not need an additional dose when they enter school. Children without documentation of adequate vaccination against measles, rubella, and mumps or other acceptable evidence of immunity to these diseases when they enter school should be admitted after receipt of the first dose of MMR. A second dose should be administered as soon as possible, but no less than 4 weeks after the first dose.

VACCINATION OF ADULTS

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. With the exception of women who might become pregnant (see rubella chapter, p. 132) and persons who work in medical facilities, birth before 1957 generally can be considered acceptable evidence of immunity to measles, rubella, and mumps.

Certain groups of adults may be at increased risk for exposure to measles and should receive special consideration for vaccination. These persons include persons attending colleges and other post-high school educational institutions, persons working in medical facilities, and international travelers.

Colleges and other post-high school educational institutions are potential high risk areas for measles, rubella, and mumps transmission because of large concentrations of susceptible persons. Prematriculation vaccination requirements for measles immunity have been shown to significantly decrease the risk of measles outbreaks on college campuses where they are implemented and enforced. **Colleges, universities, technical and vocational schools, and other institutions for post-high school education should require documentation of two doses of MMR vaccine** or other acceptable evidence of measles, rubella, and mumps immunity before entry.

Students who have no documentation of live measles, rubella, or mumps vaccination or other acceptable evidence of measles, rubella, and mumps immunity at the time of enrollment should be admitted to classes only after receiving the first dose of MMR. A second dose of MMR should be administered no less than 4 weeks (*i.e.*, minimum of 28 days) later. Students with evidence of prior receipt of only one dose of MMR or other measles-containing vaccine on or after their first birthday should receive a second dose of MMR, provided at least 4 weeks have elapsed since their previous dose.

Persons who work in **medical facilities** are at higher risk for exposure to measles than the general population. Between 1985 and 1991, at least 795 measles cases occurred in adult healthcare workers, including nurses, physicians, laboratory and radiology technicians, clerks, assistants and students. An overall decline in measles incidence occurred after the 1989-91 measles resurgence with a total of 36 cases during 1993-96 occurring among persons working in medical facilities. However, transmission in a medical facility occurred in 15 of the 75 measles outbreaks reported during 1993-1996.

All persons who work within medical facilities should have evidence of immunity to measles and rubella. Because any healthcare worker (*i.e.*, medical or non-medical, paid or volunteer,

Adults at Increased Risk of Measles

- College students
- International travelers
- Healthcare personnel

Measles Immunity in Healthcare Personnel

- All persons who work in medical facilities should be immune to measles

full time or part time, student or non-student, with or without patient-care responsibilities) who is measles or rubella susceptible can contract and transmit these diseases, all medical facilities (*i.e.*, inpatient and outpatient, private and public) should ensure measles and rubella immunity among those who work within their facilities (a possible exception might be a facility that treats only elderly patients considered at low risk for measles and rubella and their complications).

Adequate vaccination for measles and rubella for healthcare workers born during or after 1957 consists of two doses of a live measles-containing vaccine and at least one dose of a live rubella-containing vaccine. Healthcare workers needing a second dose of measles-containing vaccine should be revaccinated at least 4 weeks after their first dose.

Although birth before 1957 is generally considered acceptable evidence of measles and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to unvaccinated workers born before 1957 who do not have a history of prior measles disease or laboratory evidence of measles immunity, and those without laboratory evidence of rubella immunity.

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective. Serologic testing is appropriate only if tracking systems are used to ensure that tested persons who are identified as susceptible are subsequently vaccinated in a timely manner. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity. If the return and timely vaccination of those screened cannot be assured, serologic testing before vaccination should not be done.

Persons who travel outside of the United States are at increased risk of exposure to measles. Measles is endemic or epidemic in many countries throughout the world. Although proof of immunization is not required for entry into the United States or any other country, persons traveling or living abroad should have evidence of measles immunity. Adequate vaccination of persons who travel outside the United States is two doses of MMR.

REVACCINATION

Revaccination is recommended for certain persons. The following groups of persons should be considered unvaccinated and should receive at least one dose of measles vaccine: persons (1) vaccinated before the first birthday, (2) vaccinated with killed measles vaccine (KMV), (3) vaccinated with KMV followed by live vaccine less than 4 months after the last dose of KMV, (4) vaccinated prior to 1968 with an unknown type of vaccine (the vaccine may have been KMV), (5) or vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type (revaccination not necessary if IG was given with Edmonston B vaccine).

Measles Vaccine Indications for Revaccination

- Vaccinated before the first birthday
- Vaccinated with killed measles vaccine
- Vaccinated prior to 1968 with an unknown type of vaccine
- Vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type

POSTEXPOSURE PROPHYLAXIS

Live measles vaccine provides permanent protection and may prevent disease if given within 72 hours of exposure. **Immune globulin (IG)** may prevent or modify disease and provide temporary protection if given within 6 days of exposure. The dose is 0.25 ml/kg body weight, with a maximum of 15 ml intramuscularly. The recommended dose of IG for immunocompromised persons is 0.5ml/kg of body weight (maximum 15 ml) intramuscularly. IG may be especially indicated for susceptible household contacts of measles patients, particularly contacts <1 year of age (for whom the risk of complications is highest). If the child is 12 months of age or older, live measles vaccine should be given about 5 months later when the passive measles antibodies have waned. IG should not be used to control measles outbreaks.

MEASLES IMMUNITY

Persons generally can be considered immune to measles if they 1) were born before 1957, 2) have documentation of physician-diagnosed measles, 3) serologic evidence of immunity to measles, or 4) have documentation of adequate vaccination. Criteria for adequate vaccination depend on the person's age. In general, adequate vaccination for preschool-aged children (12 months of age and older) is one dose of MMR. For school- and college-age children, adequate vaccination is two doses of MMR.

Persons working in medical settings are at higher risk of measles than the general population. As a result, adequate vaccination for persons born during or after 1957 who work in medical facilities consists of 2 doses of MMR or other live measles-containing vaccine separated by at least 4 weeks with the first dose administered no earlier than the first birthday. Although birth before 1957 is generally considered acceptable evidence of measles immunity, measles has occurred in some unvaccinated persons born before 1957. Medical facilities should consider recommending a dose of MMR for unvaccinated workers born before 1957 who lack a history of measles disease or laboratory evidence of measles immunity.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental history of vaccination is not considered adequate documentation. A healthcare worker should not provide an immunization record for a patient unless that healthcare worker has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination status and receipt of all vaccinations should be documented in the patient's permanent medical record and in a vaccination record held by the individual.

Measles Immunity

- Born before 1957
- Documentation of physician-diagnosed measles
- Serologic evidence of immunity
- Documentation of receipt of measles-containing vaccine

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

ADVERSE REACTIONS FOLLOWING VACCINATION

Adverse reactions following measles vaccine (except allergic reactions) represent replication of measles vaccine virus with subsequent mild illness. These events occur 5-12 days postvaccination and only occur in persons who are susceptible to infection. There is no evidence of increased risk of adverse reactions following MMR vaccination in persons who are already immune to the diseases.

Fever is the most common adverse reaction following MMR vaccination. Although measles, rubella, and mumps vaccines may cause fever after vaccination, the measles component of MMR vaccine is most often associated with this adverse reaction. After MMR vaccination, 5%-15% of susceptible persons develop a temperature of $\geq 103^{\circ}\text{F}$ ($\geq 39.4^{\circ}\text{C}$) usually occurring 7-12 days after vaccination and generally lasting 1-2 days. Most persons with fever are otherwise asymptomatic.

Measles- and rubella-containing vaccines, including MMR, may cause a transient **rash**. Rashes, usually appearing 7-10 days after MMR or measles vaccination, have been reported in approximately 5% of vaccinees.

MMR vaccine may rarely cause **thrombocytopenia** (low platelet count) within the 2 months after vaccination. Estimates of the frequency of clinically apparent thrombocytopenia from Europe are 1 case per 30,000 to 40,000 vaccinated susceptible persons, with a temporal clustering of cases occurring 2 to 3 weeks after vaccination. The clinical course of these cases was usually transient and benign, although hemorrhage occurred rarely. The risk for thrombocytopenia during rubella or measles infection is much greater than the risk after vaccination. Based on case reports, the risk for MMR-associated thrombocytopenia may be higher for persons who have previously had immune thrombocytopenic purpura, particularly for those who had thrombocytopenic purpura after an earlier dose of MMR vaccine.

Transient **lymphadenopathy** sometimes occurs following receipt of MMR or other rubella-containing vaccine and **parotitis** has been reported rarely following receipt of MMR or other mumps-containing vaccine.

Arthralgias and other **joint symptoms** are reported in up to 25% of susceptible adult women given MMR vaccine. This adverse reaction is associated with the rubella component (see Rubella, Chapter 11, for more details).

Allergic reactions following the administration of MMR or any of its component vaccines are rare. Most of these reactions are minor and consist of a wheal and flare or urticaria at the injection site. Immediate, anaphylactic reactions to MMR or its component vaccines are extremely rare. Allergic reactions including rash, pruritus, and purpura have been temporally associated with mumps vaccination, but are uncommon and usually mild and of brief duration.

To date there is no convincing evidence that any vaccine causes **autism** or autism spectrum disorder. Concern has been raised about a possible relation between MMR vaccine and autism by some parents of children with autism. Symptoms of autism are often noticed by parents during the second year of life, and may follow administration of MMR by weeks or months. Two independent nongovernmental groups, the Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP) have reviewed the evidence regarding a potential link between autism and MMR vaccine. Both groups independently concluded that available evidence does not support an association, and that the U.S. should continue its current MMR vaccination policy. Additional research on the cause of autism is needed.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

Persons who have experienced a severe allergic reaction (*i.e.*, hives, swelling of the mouth or throat, difficulty breathing, hypotension, shock) following a prior dose of measles vaccine or to a vaccine component (*e.g.*, gelatin, neomycin), should generally not be vaccinated with MMR.

In the past, persons with a history of anaphylactic reactions following egg ingestion were considered to be at increased risk of serious reactions after receipt of measles- or mumps-containing vaccines, which are produced in chick embryo fibroblasts. However, recent data suggest that anaphylactic reactions to measles- and mumps-containing vaccines are not associated with hypersensitivity to egg antigens, but to other components of the vaccines (such as gelatin). The risk for serious allergic reactions following receipt of these vaccines by egg-allergic persons is extremely low and skin-testing with vaccine is not predictive of allergic reaction to vaccination. Therefore, MMR may be administered to egg-allergic children without prior routine skin testing or the use of special protocols.

MMR vaccine does not contain penicillin. A history of penicillin allergy is not a contraindication to vaccination with MMR or any other U.S. vaccine.

Women known to be pregnant should not receive measles vaccine. Pregnancy should be avoided for 4 weeks following MMR vaccine. Close contact with a pregnant woman is **NOT** a contraindication to MMR vaccination of the contact. Breastfeeding is **NOT** a contraindication to vaccination of either the woman or the breast-feeding child.

Replication of vaccine viruses can be prolonged in persons who are **immunosuppressed or immunodeficient**. Severe immunosuppression can be due to a variety of conditions, including congenital immunodeficiency, HIV infection, leukemia, lymphoma, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids. Evidence based on case reports has linked measles vaccine virus infection to subsequent

MMR Vaccine Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product

Measles and Mumps Vaccines and Egg Allergy

- Measles and mumps viruses grown in chick embryo fibroblast culture
- Studies have demonstrated safety of MMR in egg allergic children
- Vaccinate without testing

Measles Vaccine and HIV Infection

- MMR recommended for persons with asymptomatic and mildly symptomatic HIV infection
- NOT recommended for those with evidence of severe immunosuppression
- Prevacination HIV testing not recommended

death in at least six severely immunocompromised persons. For this reason, **patients who are severely immunocompromised for any reason should not be given MMR vaccine.** Healthy susceptible close contacts of severely immunocompromised persons should be vaccinated.

In general, persons receiving **large daily doses of corticosteroids** (≥ 2 mg/kg per day or ≥ 20 mg per day of prednisone) for 14 days or more should not receive MMR vaccine because of concern about vaccine safety. MMR and its component vaccines should be avoided for at least one month after cessation of high dose therapy. Persons receiving low dose or short course (<14 days) therapy, alternate-day treatment, maintenance physiologic doses, or topical, aerosol, intra-articular, bursal, or tendon injections may be vaccinated. Although persons receiving high doses of systemic corticosteroids daily or on alternate days during an interval of less than 14 days generally can receive MMR or its component vaccines immediately after cessation of treatment, some experts prefer waiting until two weeks after completion of therapy.

Patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive MMR or its component vaccines.

Measles disease may be severe in persons with **HIV infection.** Available data indicate that vaccination with MMR has not been associated with severe or unusual adverse reactions in HIV-infected persons without evidence of severe immunosuppression, although antibody responses have been variable. MMR vaccine is recommended for all asymptomatic HIV-infected persons, and should be considered for symptomatic persons who are not severely immunosuppressed. Asymptomatic children do not need to be evaluated and tested for HIV infection before MMR or other measles-containing vaccines are administered. A theoretical risk of an increase (probably transient) in HIV viral load following MMR vaccination exists because such an effect has been observed with other vaccines. The clinical significance of such an increase is not known.

MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression (see table), primarily because of a report of

Age-specific CD4+ T-lymphocyte count and percent of total lymphocytes as criteria for severe immunosuppression in HIV-infected persons.

Criteria	age <12 months	age 1-5 years	age 6-12 years	age ≥ 13 years
Total CD4+ T-lymphocytes	<750 per μ L	<500 per μ L	<200 per μ L	<200 per μ L
OR	OR	OR	OR	OR
CD4+ T-lymphocytes (as % of total lymphocytes)	<15%	<15%	<15%	<14%

measles pneumonitis in a recipient of measles vaccine who had severe HIV-related immunosuppression. Persons with **moderate or severe acute illness** should not be vaccinated until the illness has improved or resolved. This precaution is intended to prevent complicating the management of an ill patient

with a potential vaccine adverse event, such as fever. Minor illness (*e.g.*, otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illness are not contraindications to measles vaccination. One recent study suggested that seroconversion to measles vaccine was reduced in children with upper respiratory infections. However, multiple previous and subsequent studies have not confirmed this finding.

Receipt of antibody-containing blood products (*e.g.*, immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion to measles vaccine. The length of time that such passively acquired antibody persists depends on the concentration and quantity of blood product received. For instance, vaccination is recommended to be delayed for 3 months following receipt of immune globulin for prophylaxis of hepatitis A; a 7-11 month delay is recommended following administration of intravenous immune globulin, depending on the dose. For more information, see the chapter on General Recommendations on Immunization, and Measles Vaccine and the Antibody Table in Appendix A.

Persons who have a history of thrombocytopenic purpura or **thrombocytopenia** may be at increased risk for developing clinically significant thrombocytopenia after MMR vaccination. No deaths have been reported as a direct consequence of vaccine-induced thrombocytopenia. The decision to vaccinate with MMR depends on the benefits of immunity to measles, mumps, and rubella and the risks for recurrence or exacerbation of thrombocytopenia after vaccination or during natural infection with measles or rubella. The benefits of immunization are usually greater than the potential risks, and administration of MMR vaccine is justified, because of the even greater risk for thrombocytopenia after measles or rubella disease. However, deferring a subsequent dose of MMR vaccine may be prudent if the previous episode of thrombocytopenia occurred within 6 weeks after the previous dose of the vaccine. Serologic evidence of measles immunity in such persons may be sought in lieu of MMR vaccination.

Tuberculin testing (PPD) is not a prerequisite for vaccination with MMR or other measles-containing vaccine. PPD testing has no effect on the response to MMR vaccination. However, measles vaccine (and possibly mumps, rubella, and varicella vaccines) may transiently suppress the response to PPD in a person infected with *Mycobacterium tuberculosis*. If tuberculin skin testing is needed at the same time as administration of measles-containing vaccine, PPD and vaccine can be administered at the same visit. Simultaneously administering PPD and measles-containing vaccine does not interfere with reading the PPD result at 48-72 hours and ensures that the person has received measles vaccine. If the measles-containing vaccine has been administered recently, PPD screening should be delayed at least 4 weeks after vaccination. A delay in administering PPD will remove the concern of any theoretical but transient suppression of PPD reactivity from the vaccine. PPD screening can be performed and read before administering the measles-containing

PPD and Measles Vaccine

- Apply PPD at same visit as MMR
- Delay PPD ≥ 4 weeks if MMR given first
- Apply PPD first - give MMR when skin test read

vaccine. This option is the least favored because it will delay receipt of the vaccine.

VACCINE STORAGE AND HANDLING

Measles vaccine and MMR must be shipped with refrigerant to maintain 10°C (50°F) or less at all times. Vaccine must be refrigerated immediately on arrival and protected from light at all times. The vaccine must be stored at refrigerator temperature (2°-8°C [35°-46°F]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature.

After reconstitution, measles and MMR vaccines must be stored at refrigerator temperature and protected from light. Reconstituted vaccine should be used immediately. If reconstituted vaccine is not used within 8 hours it must be discarded.

MEASLES VIRUS ISOLATION

The availability of a sensitive cell line (B95a) for isolation of measles virus from clinical specimens and the establishment of automated DNA sequencing techniques have allowed for rapid genetic characterization of a large number of wild type strains of measles virus. This database of sequence information now makes it possible to use molecular epidemiological techniques to identify the source of wild type viruses and to rapidly differentiate between wild type and vaccine strains. With progress toward elimination of measles in the U.S., it is critical to examine virus isolates from as many outbreaks as possible in order to identify the source of the virus.

Virus isolation and genetic characterization can take several months to complete. Therefore, **diagnosis of measles should always be based on detection of measles-specific IgM in serum.** The IgM-capture EIA test can be completed in one day. Specimens for virus isolation can and should be taken at the same time that serum is obtained, since a delay in collection will reduce the chance of isolating the virus. However, **urine or nasopharyngeal or throat swab specimens should not be substituted for serum specimens for measles diagnosis.**

A detailed protocol for collection and transport of specimens for measles virus is available on the CDC web site at http://www.cdc.gov/ncidod/dvrd/revb/measles/viral_isolation.htm.

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